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**UNITED STATES DISTRICT COURT**
**DISTRICT OF NEW JERSEY**

| | |
|---|---|
| **PROMETHEUS LABORATORIES INC.,**<br><br>**Plaintiff,**<br><br>**v.**<br><br>**ROXANE LABORATORIES, INC.,**<br><br>**Defendant.** | **Civil Action No. _____**<br><br>**COMPLAINT FOR PATENT INFRINGEMENT**<br><br>**(Filed Electronically)** |

Plaintiff Prometheus Laboratories Inc. ("Prometheus"), by its undersigned attorneys, for its Complaint against defendant Roxane Laboratories, Inc. ("Roxane"), alleges as follows:

## Nature of the Action

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. §100, *et seq.*, arising from Roxane's filing of an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market a generic version of Prometheus' LOTRONEX® drug product prior to the expiration of United States Patent No. 6,284,770 (the "'770 patent") owned by Prometheus.

## The Parties

2. Plaintiff Prometheus is a corporation organized and existing under the laws of the State of California, having a principal place of business at 9410 Carroll Park Drive, San Diego, California 92121.

3. On information and belief, defendant Roxane is a corporation organized under the laws of Nevada, having a principal place of business at 1809 Wilson Road, Columbus, Ohio 43228.

4. On information and belief, Roxane is registered to do business in the State of New Jersey, and maintains a registered agent for service of process in New Jersey. On information and belief, Roxane regularly transacts business within this judicial district. Further, on information and belief, Roxane develops numerous generic drugs for sale and use throughout the United States, including in this judicial district. On information and belief, Roxane has litigated patent cases in this district in the past without contesting personal jurisdiction, and, in at least some of those actions, Roxane has asserted counterclaims.

## Jurisdiction and Venue

5. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

6. This Court has personal jurisdiction over Roxane by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. On information and belief, Roxane has purposefully availed itself of this forum by, among other things, making, shipping, using, offering to sell or selling, or causing others to use, offer to sell, or sell, pharmaceutical products in the State of New Jersey and deriving revenue from such activities. Further, on information and belief, Roxane has customers in the State of New Jersey.

7. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

## The Patent In Suit

8. On September 4, 2001, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '770 patent, entitled "Medicaments for the treatment of non-constipated female irritable bowel syndrome" to inventors Allen Wayne Mangel and Allison Ruth Northcutt. The '770 patent was subsequently subject to reexamination proceedings before the USPTO that resulted in the cancellation or amendment of all of the original claims of that patent. On October 19, 2010, the USPTO duly and lawfully issued a reexamination certificate for the '770 patent. A copy of the '770 patent and its reexamination certificate are attached hereto as Exhibit A.

## The LOTRONEX® Drug Product

9. Prometheus holds an approved New Drug Application ("NDA") under Section 505(a) of the FFDCA, 21 U.S.C. § 355(a), for alosetron hydrochloride tablets (NDA No. 21-107), which it sells under the trade name LOTRONEX®. The reexamined claims of the '770 patent cover, *inter alia*, methods of use and administration of alosetron or a pharmaceutically acceptable derivative thereof. Prometheus owns the '770 patent.

10. Following reexamination, the '770 patent was properly listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to LOTRONEX® pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations.

## Acts Giving Rise to this Suit

11. Pursuant to Section 505 of the FFDCA, Roxane filed ANDA No. 200-652 ("Roxane's ANDA") seeking approval to engage in the commercial use, manufacture, sale, offer for sale or importation of 0.5 mg and 1.0 mg alosetron hydrochloride tablets ("Roxane's Proposed Products"), before the reexamined '770 patent expires.

12. In connection with the filing of its ANDA as described in the preceding paragraph, Roxane has provided a written certification to the FDA, as called for by Section 505 of the FFDCA, alleging that the claims of the reexamined '770 patent are invalid, unenforceable, and/or will not be infringed by the activities described in Roxane's ANDA.

13. No earlier than January 28, 2011, Prometheus received written notice from Roxane concerning Roxane's ANDA certification ("Roxane's Notice Letter") relating to the reexamined '770 patent. Roxane's Notice Letter alleged that the claims of the reexamined '770 patent are invalid, unenforceable, and/or will not be infringed by the activities described in Roxane's ANDA. Roxane's Notice Letter also informed Prometheus that Roxane seeks approval to market Roxane's Proposed Products before the reexamined '770 patent expires. This was the first, and only, notification sent by Roxane that addressed the reexamined claims of the '770 patent.

**Count for Infringement of the '770 Patent**

14. Plaintiff repeats and realleges the allegations of paragraphs 1-13 as though fully set forth herein.

15. Roxane's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of alosetron hydrochloride tablets, prior to the expiration of the reexamined '770 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

16. On information and belief, in connection with the filing of its ANDA as described in the preceding paragraph, Roxane has provided a written certification to the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), alleging that the claims of the reexamined '770 patent are invalid, unenforceable, and/or will not be infringed by the activities described in Roxane's ANDA.

17. No earlier than January 28, 2011, Prometheus received written notice of Roxane's Paragraph IV Certification regarding the reexamined '770 patent. Roxane's Notice Letter alleged that the claims of the reexamined '770 patent are invalid, unenforceable, and/or will not be infringed by the activities described in Roxane's ANDA. Roxane's Notice Letter also informed Prometheus that Roxane seeks approval to market Roxane's Proposed Products before the reexamined '770 patent expires. This was the first, and only, notification sent by Roxane that addressed the reexamined claims of the '770 patent.

18. There is a justiciable controversy between the parties hereto as to the infringement of the reexamined '770 patent.

19. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will infringe the reexamined '770 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Products in the United States.

20. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will induce infringement of the reexamined '770 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Products in the United States. On information and belief, upon FDA approval of Roxane's ANDA, Roxane will intentionally encourage acts of direct infringement with knowledge of the reexamined '770 patent and knowledge that its acts are encouraging infringement.

21. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will contributorily infringe the reexamined '770 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Products in the United States. On information and belief, Roxane has had and continues to have knowledge that

Roxane's Proposed Products are especially adapted for a use that infringes the reexamined '770 patent and that there is no substantial non-infringing use for Roxane's Proposed Products.

22. Prometheus will be substantially and irreparably damaged and harmed if Roxane's infringement of the reexamined '770 patent is not enjoined.

23. Prometheus does not have an adequate remedy at law.

24. This case is an exceptional one, and Prometheus is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**PRAYER FOR RELIEF**

WHEREFORE, Plaintiff Prometheus respectfully requests the following relief:

(A) A Judgment be entered that Roxane has infringed the '770 patent by submitting ANDA No. 200-652;

(B) A Judgment be entered that Roxane has infringed, and that Roxane's making, using, selling, offering to sell, or importing Roxane's Proposed Products will infringe one or more claims of the '770 patent;

(C) An Order that the effective date of FDA approval of ANDA No. 200-652 be a date which is not earlier than the later of the expiration of the '770 patent, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Roxane and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, selling, offering to sell, or importing Roxane's Proposed Products until after the expiration of the '770 patent, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(E) A permanent injunction be issued, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Roxane, its officers, agents, attorneys and employees, and those acting in privity or concert with them, from practicing any methods as claimed in the '770 patent, or

from actively inducing or contributing to the infringement of any claim of the '770 patent, until after the expiration of the '770 patent, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(F) A Declaration that the commercial manufacture, use, importation into the United States, sale, or offer for sale of Roxane's Proposed Products will directly infringe, induce and/or contribute to infringement of the '770 patent;

(G) To the extent that Roxane has committed any acts with respect to the methods claimed in the '770 patent, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), that Plaintiff Prometheus be awarded damages for such acts;

(H) If Roxane engages in the commercial manufacture, use, importation into the United States, sale, or offer for sale of Roxane's Proposed Products prior to the expiration of the '770 patent, a Judgment awarding damages to Plaintiff Prometheus resulting from such infringement, together with interest;

(I) Attorneys' fees in this action as an exceptional case pursuant to 35 U.S.C. § 285;

(J) Costs and expenses in this action; and

(K) Such further and other relief as this Court may deem just and proper.

Dated: March 4, 2011

By: s/ Charles M. Lizza

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**CERTIFICATION PURSUANT TO L. CIV. R. 11.2**

I hereby certify that the matter captioned, *Prometheus Laboratories Inc. v. Roxane Laboratories, Inc.*, Civil Action No. 11-230 (FSH)(PS), is related to the matter in controversy because the matter in controversy involves the same plaintiff, the same defendant, and in both cases, the defendant is seeking FDA approval to market a generic version of the same alosetron hydrochloride drug products.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: March 4, 2011

By: s/ Charles M. Lizza

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# EXHIBIT A

US006284770B1

(12) **United States Patent**
**Mangel et al.**

(10) **Patent No.: US 6,284,770 B1**
(45) **Date of Patent: Sep. 4, 2001**

(54) **MEDICAMENTS FOR THE TREATMENT OF NON-CONSTIPATED FEMALE IRRITABLE BOWEL SYNDROME**

(75) Inventors: **Allen Wayne Mangel**, Chapel Hill; **Allison Ruth Northcutt**, Raleigh, both of NC (US)

(73) Assignee: **Glaxo Wellcome Inc.**, Research Triangle Park, NC (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/529,050**

(22) PCT Filed: **Oct. 5, 1998**

(86) PCT No.: **PCT/EP98/06278**

§ 371 Date: **Apr. 5, 2000**

§ 102(e) Date: **Apr. 5, 2000**

(87) PCT Pub. No.: **WO99/17755**

PCT Pub. Date: **Apr. 15, 1999**

(30) **Foreign Application Priority Data**

Oct. 7, 1997 (GB) ..... 9721139

(51) **Int. Cl.**[7] ..... **A61K 31/437**

(52) **U.S. Cl.** ..... **514/292**; 514/183; 514/230.5; 514/254.06; 514/284; 514/304; 514/305; 514/306; 514/394; 514/397

(58) **Field of Search** ..... 514/292, 183, 514/254.06, 284, 304, 305, 306, 230.5, 394, 397

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*Primary Examiner*—Phyllis G. Spivack
(74) *Attorney, Agent, or Firm*—Lorie Ann Morgan

(57) **ABSTRACT**

This invention relates to the use of 5-HT3 receptor antagonists in the treatment of nonconstipated female IBS patients.

**9 Claims, No Drawings**

# MEDICAMENTS FOR THE TREATMENT OF NON-CONSTIPATED FEMALE IRRITABLE BOWEL SYNDROME

This application is a rule 371 Application of PCT/EP98/06278, filed Oct. 5, 1998, which claims priority to Great Britain Patent Application No. 9721139.5, filed Oct. 7, 1997.

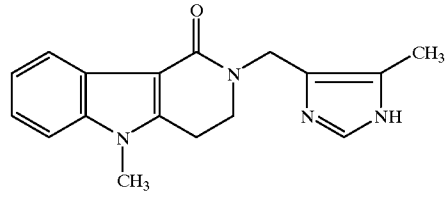
The invention relates to a new medical use for compounds which act as antagonists of 5-hydroxytryptamine (5-HT) at 5-$HT_3$ receptors.

5-$HT_3$ receptor antagonists may be identified by methods well known in the art, for example by their ability to inhibit 3-(5-methyl-1H-imidazole4-yl)-1-[1-[$^3$H]-methyl-1H-indol-3-yl]-1-propanone binding in rat entorhinal cortex homogenates (following the general procedure described by G Kilpatrick et al, Nature, 1987, 330, 746–748), and/or by their effect on the 5-HT-induced Bezold-Jarisch (B-J) reflex in the cat (following the general method described by A Butler et al, Br. J. Pharmacol., 94, 397–412 (1988)).

A number of different 5-$HT_3$ receptor antagonists have been disclosed, for example those of group A: indisetron, Ro-93777, YM-114, granisetron, talipexole, azasetron, tropisetron, mirtazapine, ramosetron, ondansetron, lerisetron, alosetron, N-3389, zacopride, cilansetron, E-3620, lintopride, KAE-393, itasetron, mosapride and dolasetron.

In UK Patent No. 2209335, incorporated herein by reference, there is disclosed, inter alia, the compound 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol4-yl) methyl]-1H-pyrido[4,3-b]indol-1-one, now known as alosetron, which may be represented by the formula (I):

(I)




and pharmaceutically acceptable salts, solvates and pharmaceutically acceptable equivalents thereof, in particular its hydrochloride salt.

5-$HT_3$ receptor antagonists are known to be useful in the treatment of a variety of conditions involving 5-$HT_3$ receptor-mediated mechanisms, including in particular emesis.

Irritable bowel syndrome (IBS) is the most common diagnosis made by gastroenterologists (1) and is characterised by abdominal pain and discomfort and altered bowel functions (2–4). To date, no laboratory or structural defects have been identified in IBS and the formal diagnosis is based upon a constellation of symptoms defined by either the Manning (5) or Rome Criteria (6).

The current understanding of the pathophysiology or etiology of IBS is limited, and no proven effective therapy is available (3,7). Moreover, many patients gain slight or even no relief from such therapies. Thus, there is a real need to develop new medicines for the treatment of IBS.

Over the last two decades compelling evidence has accumulated that a state of enhanced perception of visceral stimuli develops in patients with IBS (2,3,8–10). In balloon distension studies of the colon or rectum the threshold for sensation of pain is lower in IBS patients compared to controls, and this has been proposed as a biological marker for IBS (11). In view of the evidence for enhanced visceral perception in IBS and the frequent occurrence of pain, any agent considered to be of utility in the treatment of IBS should demonstrate effectiveness in the relief of pain.



Of the classes of therapeutic agents which have been proposed for the treatment of abdominal pain in IBS, 5-$HT_3$ receptor antagonists are among the most promising. In animal models, these agents have been shown to decrease visceral pain responses (12,13). Furthermore, the 5-$HT_3$ receptor antagonist, ondansetron, has been shown to slow colonic transit in normal volunteers (14–15). In patients with IBS ondansetron increases rectal compliance (16) and in diarrhoea-predominant IBS patients ondansetron improves stool consistency (17–19). Ondansetron also inhibits the contractile response of the colon in healthy volunteers in the early postprandial period (20), the time when many IBS patients experience symptoms. A second 5-$HT_3$ receptor antagonist, granisetron, has also been shown to produce a decrease in rectal sensitivity, and reduce post-prandial motor activity in IBS patients (21).

Alosetron is a potent and selective 5-$HT_3$ receptor antagonist, and in preliminary reports, alosetron has been shown to improve abdominal pain (22), and to slow colonic transit in IBS patients (23).

Surprisingly, it has now been found that 5-$HT_3$ receptor antagonists represent a particularly effective and well tolerated therapy in nonconstipated female IBS patients.

According to one aspect the invention therefore provides a 5-$HT_3$ receptor antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of nonconstipated female IBS.

In one preferred aspect the invention provides a 5-$HT_3$ receptor antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of diarrhea predominant female IBS.

In another preferred aspect the invention provides a 5-$HT_3$ receptor antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of alternating constipation/diarrhea IBS.

By pharmaceutically acceptable derivative is meant any pharmaceutically acceptable salt or solvate of a 5-$HT_3$ receptor antagonist or any other compound, which upon administration to the recipient is capable of providing (directly or indirectly) a 5-$HT_3$ receptor antagonist or an active metabolite or residue thereof.

In one preferred aspect the invention provides a compound of Group A or a pharmaceutically acceptable derivative thereof for use in the treatment of nonconstipated female IBS.

In a further preferred aspect the invention therefore provides alosetron or a pharmaceutically acceptable derivative thereof for use in the treatment of nonconstipated female IBS.

Suitable pharmaceutically acceptable salts of alosetron include acid addition salts formed with inorganic or organic acids (for example hydrochlorides, hydrobromides, sulphates, phosphates, benzoates, naphthoates, hydroxynaphthoates, p-toluenesulphonates, methanesulphonates, sulphamates, ascorbates, tartrates, salicylates, succinates, lactates, glutarates, glutaconates, acetates, tricarballylates, citrates, fumarates and maleates), and solvates (for example hydrates) thereof.

In a preferred embodiment of the present invention alosetron is employed in the form of its hydrochloride.

In another aspect, the invention provides the use of a 5-$HT_3$ receptor antagonist or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of nonconstipated female IBS.

In another aspect, the invention provides a method of treatment of nonconstipated female IBS which comprises administering an effective amount of a 5-$HT_3$ receptor antagonist or a pharmaceutically acceptable derivative thereof.

Within the above aspects and preferred aspects of the invention, the use of a 5-$HT_3$ receptor antagonist of Group A, more preferably alosetron, is especially preferred.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

Conveniently, a 5-$HT_3$ receptor antagonist or a pharmaceutically acceptable derivative thereof may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients. Thus a 5-$HT_3$ receptor antagonist or a pharmaceutically acceptable derivative thereof may, for example, be formulated for oral, sublingual, buccal, parenteral, rectal or intranasal administration, or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose), or in a form suitable for topical administration.

For oral administration the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrates (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid).

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

For parenteral administration the compositions may take the form of injections, conveniently intravenous, intramuscular or subcutaneous injections, for example bolus injections or continuous intravenous infusions. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, optionally with an added preservative.

The compositions for parenteral administration may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the compositions may be in dry form such as a powder, crystalline or freeze-dried solid for constitution with a suitable vehicle, e.g. sterile pyrogen-free water or isotonic saline before use. They may be presented, for example, in sterile ampoules or vials.

For rectal administration the compositions may take the form of suppositories or retention enemas.

Tablets for sub-lingual administration may be formulated in a conventional manner.

For intranasal administration, or administration by inhalation or insufflation, conventional formulations may be employed.

For topical administration the pharmaceutical compositions may be liquids, for example solutions, suspensions or emulsions presented in the form of creams or gels.

In addition to the formulations described previously, the compositions may also be formulated as a depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously, transcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compositions may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

It will be appreciated that the precise therapeutic dose of a 5-$HT_3$ receptor antagonist, expressed in the form of its free base, will depend on the age and condition of the patient and the nature of the IBS to be treated, and will be at the ultimate discretion of the attendant physician.

However, in general, effective doses for the treatment of nonconstipated female IBS patients will lie in the range of 0.001 to 500 mg, such as 0.01 to 100 mg, preferably 0.05 to 50 mg, for example 0.5 to 25 mg per unit dose, which could be administered in single or divided doses, for example, 1 to 4 times per day.

In a preferred embodiment, effective doses of alosetron for the treatment of nonconstipated female IBS patients will lie in the range of 0.01 to 100 mg, such as 0.05 to 50 mg, preferably 0.1 to 25 mg, for example 0.5, 1, 2 or 4 mg of alosetron per unit dose, which could be administered in single or divided doses, for example, 1 to 4 times per day.

The use of alosetron in the treatment of nonconstipated female IBS patients is supported by the following clinical data.

## Patients

Three hundred and seventy IBS patients were randomized for study: 80 were randomized to treatment with placebo BID, 72 to 1 mg BID alosetron, 74 to 2 mg BID alosetron, 76 to 4 mg BID alosetron and 68 to 8 mg BID alosetron. Table 1 shows the demographic characteristics for patients in all 5 treatment groups, and characteristics were similar between treatment arms. Patients were required to have symptoms which fulfilled the Rome Criteria for IBS (5) for at least 6 months. Because of the ability of 5-$HT_3$-receptor antagonists to slow colonic transit (14–15), constipation-predominant IBS patients were excluded from this study, and only patients with diarrhea-predo minant IBS or alternating constipation/diarrhoea were included.

## Study Design

Daily and weekly symptom data were collected using a recently described electronic touch4one telephone based system (24,25). Patients underwent a 2 week screening period with no IBS treatment to ensure sufficient baseline level of abdominal pain as well as compliance with the data collection system. Pain was assessed daily on a 5 point scale (0=none; 1=mild; 2=moderate; 3=intense; 4=severe). Average baseline pain over the 2 week screening period was required to be between 1.5–3.3, inclusive, and at least 4 days with at least moderate pain was required for enrolment into the study. Stool consistency data were also collected (1=very hard; 2=hard; 3=formed; 4=loose; and 5=watery). During the screening period an average stool consistency score of $\geqq$2.5 was required for entry into the study in order to exclude those with predominant constipation.

Following the screening period, eligible patients were randomized with equal allocation to 12 weeks of study

medication (BID) of placebo or alosetron 1, 2, 4 or 8 mg taken prior to meals. Patients were followed for 2 weeks post-treatment. During the screening period, treatment phase and follow-up period, patients were asked daily questions about their IBS symptoms. Once every 7 days, during the treatment phase of the study, patients responded to an additional question as to whether they had obtained adequate relief of their IBS-related abdominal pain and discomfort during the previous 7 days.

### Statistics

For this study, a responder was prospectively defined as a patient who completed the treatment phase of the study and reported adequate relief of their IBS pain and discomfort for at least 6 weeks. Responders for adequate relief have been shown to display a strong correlation with improvement in abdominal pain, bowel function and quality of life as compared to nonresponders (26). In addition, a monthly responder was defined as a patient who reported adequate relief of their IBS pain and discomfort for at least 2 weeks per month. For the monthly analysis, a last observation carried forward procedure was employed, whereby a month with all missing weeks was assigned the number of weeks with adequate relief from the previous non-missing month. Thus, this analysis satisfied the Intent-to-Treat principle by including all patients and months. Treatment groups were compared for the proportion of patients defined as responders, for both endpoints, using a Mantel-Haenszel test stratified for investigator cluster. Finally, the proportion of weeks with adequate relief was compared between treatment groups using a log-rank test.

Daily stool consistency scores and daily number of bowel movements were averaged over the baseline, weekly for weeks 1–4, and monthly (weeks 1–4, 5–8, and 9–12) intervals. In addition, the proportion of days patients experienced a sense of urgency was calculated over the monthly and weekly intervals. For the monthly intervals, the treatment groups were compared for change from baseline using a van Elteren test adjusted for investigator cluster. For the weekly intervals, the treatment groups were compared at each week using a van Elteren test adjusted for investigator cluster.

Adequate Relief of Pain and Discomfort

| | Alosetron (mg BID) | | | | |
|---|---|---|---|---|---|
| % Responders | Placebo | 1 | 2 | 4 | 8 |
| FEMALE | 33 | 60 | 59 | 51 | 52 |
| MALE | 53 | 20 | 50 | 54 | 52 |

Examination of each dose of alosetron showed a greater proportion of female responders for adequate relief as compared with placebo. The largest treatment effect occurred with 1 mg BID alosetron where 27% more responders were observed as compared to that seen with placebo (33% placebo vs 60% alosetron; p=0.013). A similar result was observed with 2 mg BID alosetron where 59% responders were seen (p=0.026). No meaningful improvement relative to placebo was seen in the male population with any dose of alosetron. However, the placebo response in males was substantially greater than that seen in females.

| | Alosetron (mg BID) | | | | |
|---|---|---|---|---|---|
| % Weeks with adequate relief | Placebo | 1 | 2 | 4 | 8 |
| FEMALE | 33 | 58 | 50 | 50 | 50 |

The proportion of weeks with adequate relief was also evaluated. Placebo treated female patients had a median 33% of weeks with adequate relief. With 1 mg BID alosetron, female patients reported adequate relief for a median 58% of the weeks (p=0.039). In the treatment groups receiving greater than 1 mg alosetron (i.e., 2 mg, 4 mg and 8 mg BID) female patients reported having adequate relief for a median 50% of the weeks with each of the doses of alosetron. By contrast, male patients received no meaningful benefit with respect to the proportion of weeks with adequate relief with alosetron.

| | Monthly Intervals | | |
|---|---|---|---|
| % Responders | 1 | 2 | 3 |
| Placebo | 32 | 42 | 36 |
| Alosetron 1 mg BID | 53 | 62 | 60 |

In order to identify how rapidly alosetron produces adequate relief, we analyzed adequate relief during each of the three months of the study with 1 mg BID alosetron, statistically significant improvement occurred for female patients during each month. Increases of 21%, 20% and 24% above placebo were seen at months 1,2 and 31 respectively. Alosetron 1 mg was superior to the other alosetron (2,4, or 8 mg) evaluated. No improvement relative to placebo was seen among males at any month, with any dose of alosetron.

### Improvement in Bowel Habits

In females patients, most doses of alosetron significantly improved stool consistency, bowel movement frequency and the proportion of days with urgency as compared to placebo (Table 2). For each of these parameters, a statistically significant benefit over placebo was achieved after 1 week of treatment and benefit persisted throughout the remainder of the 12 week treatment period. Among males, no significant improvement over placebo was seen in the bowel-related functions with the exception of stool consistency. Stool consistency in males improved significantly with doses of alosetron higher than 1 mg BID.

These results demonstrate that alosetron significantly improved abdominal pain and bowel function in female IBS patients. Alosetron also significantly improved, in female patients, three clinically relevant bowel related functions: number of bowel movements per day, stool consistency, and sense of urgency. All of these parameters were significantly improved within the first week of treatment and were sustained throughout the three month study.

Surprisingly, alosetron-mediated improvement in the efficacy parameters, with the exception of hardening in stool consistency, were found to occur only in females.

Based upon the results of the present study, alosetron appears to represent an effective and well tolerated therapy in nonconstipated female IBS patients.

TABLE 1

Demographic Characteristics

| Characteristic | Placebo | Alosetron BID 1 mg | 2 mg | 4 mg | 8 mg |
|---|---|---|---|---|---|
| n | 80 | 72 | 74 | 76 | 68 |
| Age (yrs) | 43.3 ± 14.9 | 44.7 ± 13.5 | 43.9 ± 14.9 | 44.3 ± 11.9 | 45.1 ± 14.8 |
| Sex | | | | | |
| Male | 21 (26%) | 19 (26%) | 23 (31%) | 21 (28%) | 28 (41%) |
| Female | 59 (74%) | 53 (74%) | 51 (69%) | 55 (72%) | 40 (59%) |
| Race | | | | | |
| Caucasian | 76 (95%) | 67 (93%) | 67 (91%) | 75 (99%) | 63 (93%) |
| Black | 3 (4%) | 3 (4%) | 4 (5%) | 0 (0%) | 0 (0%) |
| Other | 1 (1%) | 2 (3%) | 3 (4%) | 1 (1%) | 5 (6%) |
| Females | | | | | |
| Post-Menopausal | 10 (17%) | 9 (17%) | 9 (18%) | 9 (16%) | 8 (20%) |
| Sterile | 25 (42%) | 29 (55%) | 25 (49%) | 35 (64%) | 19 (48%) |
| Child-bearing Potential | 24 (41%) | 15 (28%) | 17 (33%) | 11 (20%) | 13 (33%) |
| Duration of IBS Symptoms (yrs) | 9.8 ± 10.9 | 10.3 ± 10.4 | 9.4 ± 9.9 | 9.9 ± 9.3 | 9.3 ± 7.7 |
| Baseline Pain | 2.23 ± 0.47 | 2.12 ± 0.48 | 2.11 ± 0.42 | 2.22 ± 0.48 | 2.30 ± 0.47 |

Pain score: 0 = none, 1 = mild, 2 = moderate, 3 = intense, 4 = severe

TABLE 2

Effects of Alosetron on Bowel Function In Female Patients With IBS

| Function | Placebo | Alosetron BID 1 mg | 2 mg | 4 mg | 8 mg |
|---|---|---|---|---|---|
| (n) | (59) | (53) | (51) | (55) | (40) |
| % Days with Urgency | 54.3 ± 32.04 | 33.0 ± 28.8* | 35.9 ± 34.4** | 37.8 ± 34.2* | 41.5 ± 33.6 |
| Stool # per day | 2.2 ± 1.35 | 1.4 ± 1.0* | 1.7 ± 0.9* | 1.8 ± 1.2* | 1.3 ± 0.7* |
| Stool Consistency | 2.9 ± 0.69 | 2.1 ± 0.83** | 2.2 ± 0.73** | 2.4 ± 0.74** | 1.8 ± 0.64** |

mean ± SD
Data collected from week 9–12 interval
p-values are based on change from baseline
*p ≦ 0.01 with respect to placebo
**p ≦ 0.001 with respect to placebo
Consistency score: 1 = very hard, 2 = hard, 3 = formed, 4 = loose, 5 = watery

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What is claimed is:

**1**. A method of treatment of nonconstipated female IBS which comprises administering an effective amount of a 5-$HT_3$ receptor antagonist or a pharmaceutically acceptable derivative thereof selected from the group consisting of granisetron, azasetron, tropisetron, ramosetron, ondansetron, lerisetron, (R) zacopride, cilansetron, itasetron, indisetron and dolasetron and pharmaceutically acceptable derivatives thereof.

**2**. A method of treatment of nonconstipated female IBS which comprises administering an effective amount of alosetron or a pharmaceutically acceptable derivative.

**3**. A method of treatment according to claim **2** wherein alosetron is in the form of its hydrochloride.

**4**. A method of treatment of diarrhea-predominant female IBS which comprises administering an effective amount of a 5-$HT_3$ receptor antagonist or a pharmaceutically acceptable derivative thereof selected from the group consisting of granisetron, azasetron, tropisetron, ramosetron, ondansetron, lerisetron, (R) zacopride, cilansetron, itasetron, indisetron and dolasetron and pharmaceutically acceptable derivatives thereof.

**5**. A method of treatment of diarrhea-predominant female IBS which comprises administering an effective amount of alosetron or a pharmaceutically acceptable derivative thereof.

**6**. A method of treatment according to claim **5**, wherein alosetron is in the form of its hydrochloride.

**7**. A method of treatment of alternating constipation/diarrhea IBS which comprises administering an effective amount of a 5-$HT_3$ receptor antagonist or a pharmaceutically acceptable derivative thereof selected from the group consisting of granisetron, azasetron, tropisetron, ramosetron, ondansetron, lerisetron, (R) zacopride, cilansetron, itasetron, indisetron and dolasetron and pharmaceutically acceptable derivatives thereof.

**8**. A method of treatment of alternating constipation/diarrhea IBS which comprises administering an effective amount of alosetron or a pharmaceutically acceptable derivative thereof.

**9**. A method of treatment according to claim **8**, wherein alosetron is in the form of its hydrochloride.

* * * * *

US006284770C1

# (12) EX PARTE REEXAMINATION CERTIFICATE (7818th)

**United States Patent**
**Mangel et al.**

(10) **Number: US 6,284,770 C1**
(45) **Certificate Issued: Oct. 19, 2010**

(54) **MEDICAMENTS FOR THE TREATMENT OF NON-CONSTIPATED FEMALE IRRITABLE BOWEL SYNDROME**

(75) Inventors: **Allen Wayne Mangel**, Chapel Hill, NC (US); **Allison Ruth Northcutt**, Raleigh, NC (US)

(73) Assignee: **Prometheus Laboratories, Inc.**, San Diego, CA (US)

**Reexamination Request:**
No. 90/010,634, Aug. 3, 2009

**Reexamination Certificate for:**

| | |
|---|---|
| Patent No.: | **6,284,770** |
| Issued: | **Sep. 4, 2001** |
| Appl. No.: | **09/529,050** |
| Filed: | **Apr. 5, 2000** |

(22) PCT Filed: **Oct. 5, 1998**

(86) PCT No.: **PCT/EP98/06278**

§ 371 (c)(1),
(2), (4) Date: **Apr. 5, 2000**

(87) PCT Pub. No.: **WO99/17755**

PCT Pub. Date: **Apr. 15, 1999**

(30) **Foreign Application Priority Data**

Oct. 7, 1997 (GB) ..... 9721139

(51) **Int. Cl.**

| | |
|---|---|
| ***A61K 45/00*** | (2006.01) |
| ***A61K 31/00*** | (2006.01) |
| ***A61K 31/40*** | (2006.01) |
| ***A61K 31/435*** | (2006.01) |
| ***A61K 31/495*** | (2006.01) |
| ***A61K 31/47*** | (2006.01) |
| ***A61K 31/55*** | (2006.01) |
| ***A61P 1/00*** | (2006.01) |
| ***A61P 1/08*** | (2006.01) |
| ***A61P 25/04*** | (2006.01) |
| ***A61P 43/00*** | (2006.01) |

(52) **U.S. Cl.** ..... **514/292**; 514/183; 514/230.5; 514/254.06; 514/284; 514/304; 514/305; 514/306; 514/394; 514/397

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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*Primary Examiner*—Bruce Campell

(57) **ABSTRACT**

This invention relates to the use of 5-HT3 receptor antagonists in the treatment of nonconstipated female IBS patients.

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Exhibit 2—Yale, S.H. et al., "Applying Case Definition Criteria to Irritable Bowel Syndrome," *Clinical Medicine & Research,* May 2008, vol. 6, No. 1, pp. 9–16.

Exhibit 3—Tennis, P. et al., "The relationship between dosing of alosetron and discontinuation patterns reported by patients participating in a follow–up programme," *Alimentary Pharmacology & Therapeutics,* 2007, vol. 25, pp. 317–322.

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# EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

**Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.**

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims **1-4** and **7-9** are cancelled.

Claims **5-6** are determined to be patentable as amended.

New claims **10-16** are added and determined to be patentable.

**5**. A method **[**of treatment of**]** *for treating a* diarrhea-predominant female IBS **[**which comprises**]** *patient, while excluding those with predominant constipation, said method comprising:*

*assessing whether said diarrhea-predominant female IBS patient has experienced symptoms for at least six months; and*

administering an effective amount of alosetron or a pharmaceutically acceptable derivative thereof *to said patient who has experienced symptoms for at least six months, wherein said effective amount is dependent on the condition of the patient and is at the discretion of the attendant physician.*

**6**. **[**A**]** *The* method **[**of treatment**]** *for treating* according to claim **5**, wherein alosetron is in the form of its hydrochloride *salt.*



*10. The method for treating according to claim 5, further comprising assessing whether said female IBS patient has experienced at least moderate pain prior to administration of alosetron.*

*11. The method for treating according to claim 5, wherein said female IBS patient experiences improvement in stool consistency, bowel movement frequency and the proportion of days with urgency while being treated with alosetron.*

*12. The method for treating according to claim 12, wherein said female IBS patient experiences improvement within about 1 week of treatment.*

*13. A method for treating a diarrhea-predominant female IBS patient, while excluding those with predominant constipation, said method comprising:*

*assessing whether said diarrhea-predominant female IBS patient has experienced symptoms for at least six months;*

*assessing whether said nonconstipated female IBS patient experiences at least moderate baseline pain from IBS; and*

*administering an effective amount of alosetron or a pharmaceutically acceptable derivative thereof to said patient who has experienced symptoms for at least six months and who experiences at least moderate baseline pain from IBS, wherein said effective amount is dependent on the condition of the patient and is at the discretion of the attendant physician.*

*14. The method for treating according to claim 13, wherein alosetron is in the form of its hydrochloride salt.*

*15. The method for treating according to claim 13, wherein said female IBS patient experiences improvement in stool consistency, bowel movement frequency and the proportion of days with urgency while being treated with alosetron.*

*16. The method for treating according to claim 13, wherein said female IBS patient experiences improvement within about 1 week of treatment.*

* * * * *